the array to identify the location of at least a second population of bioactive agents.

33. (Amended) A method according to claim 8, 13 or 14, wherein said plurality of decoder binding ligands comprises at least a first and a second subpopulation of decoder binding ligands.

REMARKS

Claims 1-7 and 15 previously have been canceled. Claims 8-14, 16-28, and 30-35 are pending. For the Examiner's convenience a copy of the currently pending claims is attached hereto as Appendix A. A copy of the "Version to Show Changes Made" is also attached as Appendix B. Claims 8, 9, 10, 13, 14, 16, and 30-33 are amended. Claim 29 is canceled. Support for the amendments of claims 8, 9, and 10 is found throughout the specification including p. 16, lines 16-25 and p. 17, lines 14-20. Support for the amendments of claim 16 is found throughout the specification including p. 16, lines 16-25 and p. 17, lines 14-20 and in claim 2 as filed. Support for the amendments of claims 13 and 14 is found throughout the specification including claim 29. Claims 30-33 are amended for clarity and no new matter was added. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the following reasons.

RESPONSE TO REJECTIONS

Response to Rejection Under 35 U.S.C. § 102 as anticipated by Ekins *et al.*

Currently pending Claims 16-18 are rejected under 35 U.S.C. § 102 (b) and (e) as being anticipated by Ekins et al (U.S. Patent No 5,516,635) ("Ekins"). The Examiner maintains that Ekins discloses the distribution of microspheres onto a surface to form an

array upon which multiple binding assays may be performed. Moreover, the Examiner suggests that Ekins discloses that the microspheres contain bioactive agents, identifier binding ligands and decoder binding ligands which identify the bioactive agents. Applicants respectfully traverse.

Ekins is directed to binding assays employing labeled microspheres. Ekins discloses spotting a capture binding agent on a surface, adding a "developing binding material," and adding a target to the developing binding agent. Then the target is detected with labeled (preferably fluorescently labeled) microspheres. The microspheres contain a developing binding agent that binds the capture binding agent, thereby immobilizing the microspheres on the array. Particularly, in Example 5, column 13, Ekins refers to shaking immobilized microspheres, not to randomly distributing microspheres on a surface by shaking. The Examiner will please note that Figures 3, 4, and 5 are deceptive; moieties A and B are not microspheres rather, moieties A and B are spotted binding ligands and the developing binding material, respectively. Only the "M" moiety is a microsphere; thus there is no direct interaction of the microsphere with the surface.

In contrast, Claims 16-18 are directed to a method of making a microsphere array. The method includes contacting a substrate with a surface comprising discrete sites with a solution comprising a population of particles and applying energy to said substrate or solution, such that at least a subpopulation of said particles randomly associate onto sites.

As the Examiner is aware, anticipation under 35 U.S.C. § 102 requires that "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed

invention must be identically shown in a single reference." In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990).

With respect to claims 16-18 , Applicants note that Ekins fails to teach randomly distributing microspheres on a substrate. That is, the microspheres of Ekins bind to specific locations on the array because of the capture binding agent that is spotted on the array. Accordingly, Applicants submit that Ekins fails to teach every limitation and thus does not anticipate claims 16-18. Applicants respectfully request that the Examiner withdraw this rejection.

Response to Rejection Under 35 U.S.C. § 102 as anticipated by Walt *et al.*

Currently pending Claims 8-14, 16-18, and 21-35 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Walt et al (U.S. Patent No 6,023,540). The Examiner notes that Walt discloses the preparation and use of fiber optic sensors with encoded microspheres. Examiner also notes that Walt discloses fluorescent dyes bound to microspheres.

Walt discloses that different populations of microspheres are saturated with two reporter dyes of different ratios of the dyes (col. 10, lines 50-67). The populations of microspheres have optical signatures comprising these dyes that are used to encode the microspheres to identify the bioactive agents.

In contrast, the claims 8-13 provide for methods of decoding an array and specifically excludes the presence of an optical signature. Claims 8-13 rely on a bead with no optical signature, to which a decoder binding ligand binds to detect bioactive

agents. In some embodiments the decoder binding ligands bind to the bioactive agent. In some embodiments the decoder binding ligands bind to identifier binding ligands on microspheres.

Claim 14 is directed to a method of determining the presence of a target analyte in a sample, by contacting the sample with a substrate comprising discrete sites, and a population of randomly distributed microspheres. The microspheres comprise at least a first and second subpopulation, each comprising a bioactive agent, and an identifier binding ligand. Next, the presence or absence of the target analyte is determined. Finally, a plurality of decoding, binding ligands are added to the array to identify the location of a plurality of the bioactive agents.

Claims 16-18 are directed to a method lf making a microsphere array comprising contacting a substrate comprising discrete sites with a solution of a population of particles with no optical signature, and applying energy to substrate or the solution, or both, such that the particles randomly associate onto sites.

Again, anticipation under 35 U.S.C. § 102 requires that "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990).

With respect to claims 8-13, Applicants note that Walt teaches microspheres that have an optical signature, while claims 8-13 exclude an optical signature. Thus, Walt does not anticipate claims 8-13.

With respect to claim 14, Applicants note that the element of a decoding binding ligand is not described in Walt. Walt does not teach a decoder binding ligand, but a marker dye which can determine the presence of a bioactive agent, but not discriminate its location. Hence, Walt does not meet every element of claim 14.

With respect to claims 16-18, Applicants note that the population of particles in the present invention do not have an optical signature. Again, applicants note that Walt teaches microspheres with an optical signature. Accordingly, Applicants respectfully submit that the claims 16-18 are in condition for allowance. Applicants respectfully request that the Examiner withdraw the rejection.

Applicants respectfully submit that the remaining claims are ultimately dependant on allowable independent claims. Accordingly, they too are not anticipated by Walt. In light of the forgoing, Applicants respectfully request the Examiner to withdraw the rejection.

Response to Rejection Under 35 U.S.C. § 103 as anticipated by Ekins *et al.*

Claims 8-14, 21, and 23-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Ekins. The Examiner suggests that it would have been obvious to one of ordinary skill in the art to perform the Ekins assay with labeled microspheres in patterned microtitre plates with microspheres randomly distributed within each well thus resulting in the practice of the instant invention. Applicants respectfully traverse the rejection.

As described above Ekins teaches the use of non-randomly distributed, labeled

microspheres to detect a target analyte. Ekins is not directed to determining the location of the binding agents; Ekins is directed to determining the presence or absence of these agents.

Claims 8 is directed to a method of decoding an array composition and determining the presence of a target analyte in a sample, respectively. The methods include contacting a substrate with a surface comprising discrete sites, and a population of microspheres that do not comprise optical signatures.

Claim 13 is directed to methods of decoding an array and includes randomly distributing the microspheres on the surface of the array such that the discrete sites contain microspheres that do not comprise optical signatures.

Claim 14 is directed to a method of determining the presence of a target analyte in a sample, by contacting the sample with a substrate comprising discrete sites, and a population of randomly distributed microspheres.

Applicants note that there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2143).

Initially, Applicants note that all three independent claims require random

distribution of microspheres. This is in contrast to Ekins, which teaches non-random, i.e. targeted distribution of labeled microspheres. Applicants note that Ekins does not provide a motivation to modify the teaching disclosed in Ekins, because Ekins provides a detectable label to identify whether or not a particular target is immobilized on a substrate. The microspheres are thus targeted to bind to a particular site on the surface, i.e. where is target is.

In contrast, the microspheres of the present invention are distributed randomly. They associate with a site, but this invention does not require that the microsphere associate with a particular site on the surface. This is in sharp contrast to Ekins where the microspheres are in fact targeted to particular locations on the surface.

Thus, there is no motivation to modify Ekins because, if Ekins used random distribution of beads instead of targeted distribution, there would be no specificity in the signal observed on the Ekins surface. In *Dow Chemical Co. v. American Cyanamid Co.*, 2 USPQ2d 1350 (CAFC 1987), the Federal Circuit affirmed a district court holding that various patents were not invalid as obvious over a prior art reference because the prior art reference "taught away" from the inventions in those patents." Accordingly, Applicants submit that Ekins teaches away from random distribution of microspheres. As such, Applicants submit that one of skill in the art would not have been motivated to modify the teachings of Ekins.

With respect to claims 8 and 13, Applicants respectfully submit that Ekins does not teach or suggest all the claim limitations. The Applicants respectfully submit that Ekins does not teach or suggest the use of decoding binding ligands to identify the location of microspheres containing bioactive agents. Applicants further submit, as

described above, that Ekins does not teach random distribution of microspheres on a substrate, nor does it teach a patterned substrate. Finally, Applicants submit that Ekins does not teach microspheres that do not comprise an optical signature. As such, Applicants submit that the reference fails to teach each element of the claims.

With respect to claim 14, Applicants again submit that Ekins does not teach or suggest all the claim limitations. The Applicants respectfully submit that Ekins does not teach or suggest the use of decoding binding ligands to identify the location of microspheres containing bioactive agents. Applicants further submit, as described above, that Ekins does not teach random distribution of microspheres on a substrate, nor does it teach a patterned substrate. As such, Applicants submit that the reference fails to teach each element of the claims.

Accordingly, Applicants submit that the cited reference does not render the claimed invention obvious to one of skill in the art at the time the invention was made. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims as amended are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

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AppendixB: Version to Show Changes Made

8. (Amended) A method of decoding an array composition comprising
a) providing an array composition comprising:
i) a substrate with a patterned surface comprising discrete sites; and
ii) a population of microspheres comprising at least a first and a second subpopulation, wherein each subpopulation comprises a bioactive agent and do not comprise an optical signature;
wherein said microspheres are randomly distributed on said surface;
b) adding a plurality of decoding, binding ligands to said array composition to identify the location of at least a plurality of the bioactive agents.

9. (Amended) A method according to claim 8 wherein at least one subpopulation of microspheres comprises an identifier binding ligand to which a decoding, binding ligand can bind specifically .

10. (Amended) A method according to claim 8 wherein said decoding, binding ligands bind specifically to said bioactive agents.

11. A method according to claim 8 wherein said decoding, binding ligands are labeled.

12. A method according to claim 8 wherein the location of each subpopulation is determined.

13. (Amended) A method of determining the presence of a target analyte in a sample comprising:
a) contacting said sample with a composition comprising:
i) a substrate with a patterned surface comprising discrete sites; and
ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent and do not comprise an optical signature;
wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres; and
b) determining the presence or absence of said target analyte.
c) adding a plurality of decoding, binding ligands to said array composition to identify the location of at least a plurality of the bioactive agents.

14. (Amended) A method of determining the presence of a target analyte in a sample

comprising:

a) contacting said sample with a composition comprising:

i) a substrate with a surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising:

1) a bioactive agent; and

2) an identifier binding ligand that will bind a decoder binding ligand such that the identification of the bioactive agent can be elucidated;

wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres; and

b) determining the presence or absence of said target analyte.

c) adding a plurality of decoding, binding ligands to said array composition to identify the location of at least a plurality of the bioactive agents.

16. (Amended) A method of making a microsphere array comprising:

a) contacting a substrate with a surface comprising discrete sites with a solution comprising a population of particles,wherein said particles do not comprise an optical signature; and

b) applying energy to said substrate or said solution, or both, such that at least a subpopulation of said particles randomly associate onto sites.

17. A method according to claim 16 wherein said discrete sites comprise wells.

18. A method according to claim 16 wherein said energy is in the form of agitation.

19. A method according to claim 16, wherein said energy is dipping said substrate into said particles.

20. A method according to claim 19, wherein said substrate is a fiber optic bundle.

21. A method according to claim 8, 13 or 14, wherein said substrate is selected from the group consisting of glass and plastic.

22. A method according to claim 8, 13 or 14, wherein said substrate is a fiber optic bundle.

23. A method according to claim 8, 13 or 14, wherein said bioactive agent is selected

from the group consisting of nucleic acids and proteins.

24. A method according to claim 13 or 14, wherein said target analyte is a nucleic acid.

25. A method according to claim 14, wherein said decoder binding ligands comprise labels.

26. A method according to claim 8 or 14, wherein said decoder binding ligands are nucleic acids.

27. A method according to claim 8 or 14, wherein said identifier binding ligands are nucleic acids.

28. A method according to claim 8 or 14, wherein said identifier binding ligands are nucleic acids and said decoder binding ligands are nucleic acids, wherein said identifier binding ligands and said decoder binding ligands comprise substantially complementary sequences.

30. A method according to claim 8, 13 or 14 [29], wherein each of said decoder binding ligands comprise the same label, and wherein detection of said label results in the identification of the bioactive agent.

31. A method according to claim 8, 13 or 14 [29], wherein a first population of said plurality of decoder binding ligands comprises a first label and a second population of said decoder binding ligands comprises a second label.

32. A method according to claim 8, 13 or 14[29], wherein a first population of decoder binding ligands is contacted with the array to identify the location of at least a first population of bioactive agents; and

subsequently, a second population of decoder binding ligands is contacted with the array to identify the location of at least a second population of bioactive agents.

33. A method according to claim 8, 13 or 14 [29], wherein said plurality of decoder binding ligands comprises at least a first and a second subpopulation of decoder binding ligands.

34. A method according to claim 8, 13 or 14, wherein said discrete sites are wells.

35. A method according to claim 8, wherein said bioactive agents are nucleic acids.